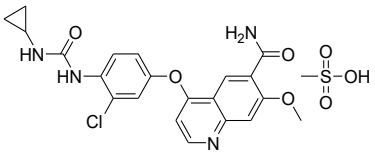
Lenvatinib Mesylate



$C_{21}H_{19}ClN_4O_4,CH_4O_3S$ Mol. Wt. 523.0

Lenvatinib Mesylate is 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methane sulphonate.

Lenvatinib Mesylate contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{21}H_{19}ClN_4O_4.CH_4O_3S$, calculated on anhydrous basis.

CAUTION –Lenvatinib Mesylate is cytotoxic, extra care required to prevent inhaling particles and exposing the skin to it.

Category. Anticancer.

Description. A white to pale reddish yellow powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *lenvatinib mesylate IPRS* or with the reference spectrum of lenvatinib mesylate.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in chromatogram obtained with the reference solution.

Tests

Methane sulphonic acid content.17.5 per cent to 19.5 per cent, calculated on anhydrous basis.

Dissolve 0.4 g in 50 ml of a mixture of 2 volumes of *dimethylsulphoxide*, 2 volumes of *methanol* and 1 volume of *water*. Titrate with *0.1 M sodium hydroxide*, determining the end point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1M sodium hydroxide* is equivalent to 0.00961 g of *methane sulphonic acid*.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture (a). Equal volumes of *methanol* and *water.*

Solvent mixture (b). 70 volumes of *methanol* and 30 volumes of *water.*

NOTE—Prepare the solutions immediately before use.

Test solution. Dissolve 25 mg of substance under examination in 40 ml of *methanol* and dilute to 100.0 ml with solvent mixture (a).

Reference solution (a). Dissolve 25 mg of *lenvatinib mesylate IPRS* in 40 ml of *methanol* and dilute to 100.0 ml with solvent mixture (a). Dilute 1.0 ml of the solution to 25.0 ml with solvent mixture (b). Further, dilute 5.0 ml of this solution to 100.0 ml with solvent mixture (b).

Reference solution (b). Dilute 3.0 ml of reference solution (a) to 10.0 ml with solvent mixture (b).

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as X-Bridge Shield RP-18),
- sample temperature: 10°,
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water,* adjusted to pH 3.25 with *dilute orthophosphoric acid*,
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
15	70	30
20	70	30
35	60	40
45	60	40
55	30	70
57	90	10
65	90	10

Name	Relative retention time	Correction factor
Descyclopropyl lenvatinib[1]	0.65	0.78
Methyl analogue of lenvatinib[2]	0.79	0.79
Lenvatinib carboxylic acid[3]	0.87	0.98
Lenvatinib (Retention time about 17 minutes)	1.00	---
Carbamate derivative of APQC[4]	1.90	1.19
Carbamoyl derivative of lenvatinib[5]	2.18	0.99
Nitrile analogue of lenvatinib[6]	2.57	1.05

[1]4-[4-(carbamoylamino)-3- chlorophenoxy]-7- methoxyquinoline-6- carboxamide
[2]4-(3-chloro-4- [(methylcarbamoyl)amino]phenoxy)-7-methoxyquinoline-6-carboxamide
[3]4-(3-chloro-4- [(cyclopropylcarbamoyl)amino]phenoxy)-7- methoxyquinoline-6- carboxylic acid
[4]phenyl (4-[(6-carbamoyl-7- methoxyquinolin-4-yl)oxy]- 2-chlorophenyl)carbamate
[5]4-(3-chloro-4- [(cyclopropylcarbamoyl)ami no]phenoxy)-N- (cyclopropylcarbamoyl)-7- methoxyquinoline-6- carboxamide
[6]1-(2-chloro-4-[(6-cyano-7- methoxyquinolin-4- yl)oxy]phenyl)-3- cyclopropylurea

Inject reference solution (a) and (b). The test is not valid unless the column efficiency is not less than 50000 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to descyclopropyl lenvatinib, methyl analogue of lenvatinib, lenvatinib carboxylic acid, carbamate derivative of APQC, carbamoyl derivative of lenvatinib and nitrile analogue of lenvatinib, each of, is not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary peaks is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Water (2.3.43). Not more than 7.5 per cent, determined on 0.2 g.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture (a). Equal volumes of *methanol* and *water.*

Solvent mixture (b). 70 volumes of *methanol* and 30 volumes of *water.*

NOTE—Prepare the solutions immediately before use.

Test solution. Dissolve 50 mg of the substance under examination in 40 ml of *methanol* and dilute to 100.0 ml with solvent mixture (a). Dilute 5.0 ml of the solution to 100.0 ml with solvent mixture (b).

Reference solution. Dissolve 50 mg of *lenvatinib mesylate IPRS* in 40 ml of *methanol* and dilute to 100.0 ml with solvent mixture (a). Dilute 5.0 ml of the solution to 100.0 ml with solvent mixture (b).

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm) (Such as X-Bridge C18),
- column temperature: 40º,
- sample temperature: 10º,
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 3.25 with *dilute orthophosphoric acid*,
  B. *acetonitrile,*

- flow rate: 1 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
8	75	25
10	35	65
15	35	65
17	75	25
25	75	25

Inject the reference solution. The test is not valid unless the column efficiency is not less than 5000 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{19}ClN_4O_4,CH_4O_3S$

Storage. Store protected from moisture, at a temperature between 2º to 8º.

Solubility (2.4.26). Very slightly soluble in *water,* practically insoluble in *ethanol*.